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Application No. (if known): 10/826,868 Attorney Docket No.: 02901/100M869-US1

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Restriction Requirement (2 pages)
Copy of Return Receipt Postcard
Copy of Utility Patent Application Transmittal (1 page)
Copy of Specification (11 pages), Claims (7 pages), Abstract (1 page)
Copy of 12 Figures (12 sheets)
Copy of Application Data Sheet (3 pages)
Copy of Preliminary Amendment (8 pages)
Copy of Certificate of Express Mail (1 page)

Atty Docket No.: 02901/100M869-US1

Inventor: Stefano Turchetta et al.

Appln: Not Yet Assigned **Filed:** Concurrently Herewith

Title: POLYMORPHOUS FORMS OF ROSIGLITAZONE MALEATE

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Documents:

Utility Patent Application Transmittal (1 page)
Specification (11 pages), Claims (7 pages), Abstract (1 page)
12 Figures (12 sheets)
Application Data Sheet (3 pages)
Preliminary Amendment (8 pages)
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19270 U.S. PTO
10/826868

041604

EV983948656-US

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Utility Patent Application Transmittal (1 page)
Specification (11 pages), Claims (7 pages), Abstract (1 page)
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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	02901/100M869-US1
First Inventor	Stefano Turchetta
Title	POLYMORPHOUS FORMS OF ROSIGLITAZONE MALEATE
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: MS Patent Application
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1. [ ] Fee Transmittal Form (e.g., PTO/SB/17) *(Submit an original, and a duplicate for fee processing)*
2. [ ] Applicant claims small entity status. See 37 CFR 1.27.
3. [X] Specification [*Total Pages* 19]
   (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
4. [X] Drawing(s) *(35 U.S.C. 113)* [*Total Sheets* 12]
5. Oath or Declaration [*Total Sheets*]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 18 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. [X] Application Data Sheet. See 37 CFR 1.76
7. [ ] CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. [ ] Assignment Papers (cover sheet & document(s))
10. [ ] 37 CFR 3.73(b) Statement *(when there is an assignee)* [ ] Power of Attorney
11. [ ] English Translation Document *(if applicable)*
12. [ ] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
13. [X] Preliminary Amendment
14. [X] Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
15. [ ] Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
16. [ ] Nonpublication Request under 35 U.S.C. 122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or its equivalent.
17. [X] Other: Certificate of Express Mail

18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*

[ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No.: _____

Prior application information: Examiner _____ *Art Unit:* _____

For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS

[X] Customer Number: 07278 *OR* [ ] Correspondence address below

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Signature		*Date*	April 14, 2004

16

05-27-05 AFW/1625

Docket No.: 02901/100M869-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stefano Turchetta et al.

Application No.: 10/826,868 Confirmation No.: 9826

Filed: April 16, 2004 Art Unit: 1625

For: POLYMORPHOUS FORMS OF ROSIGLITAZONE MALEATE Examiner: P. L. Morris

RESPONSE TO RESTRICTION REQUIREMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants thank the examiner for the telephone discussion on May 24, 2005 regarding contents of the Office Action (Election/Restriction) mailed April 25, 2005.

In the Office Action the examiner states that the restriction requirement has been based on the claims presented in the preliminary amendment filed April 16, 2004; and that there appear to be two different specifications and two different sets of claims in the application. Applicants enclose herewith true copies of the documents mailed to the Patent Office on April 16, 2004 (namely those documents identified on the stamped return receipt postcard, a copy of which is also attached). As discussed with the Examiner, the Patent Office records are incomplete and/or incorrect in that the Office appears to have an incomplete copy of the preliminary amendment mailed on April 16, 2004, and the specification on file appears to be a translation of the priority document rather than the specification and claims as mailed on April 16, 2004. Correction of the Patent Office records, both physical and electronic (Private and Public PAIR), is respectfully

requested. Applicants agree with the examiner that these discrepancies do not affect the merits of the Office Action.

In response to the restriction requirement in this application, Applicants hereby elect to prosecute claims to Invention Group II (Claims 16-25), drawn to a process of preparing, classified in class 546, subclass 268.1.

A prompt official action on the merits of the elected invention is earnestly solicited.

Dated: May 25, 2005

Respectfully submitted,

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Attorneys/Agents For Applicant

Docket No.: 02901/100M869-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stefano Turchetta et al.

Application No.: Not Yet Assigned

Filed: Concurrently Herewith

For: POLYMORPHOUS FORMS OF ROSIGLITAZONE MALEATE

FIRST PRELIMINARY AMENDMENT

MS Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 7 of this paper.

Remarks/Arguments begin on page 8 of this paper.

AMENDMENTS TO THE SPECIFICATION

On page 1, after the Title, please insert:

-- CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority of U. S. Provisional Patent Application Serial No. 60/472,756, filed May 21, 2003, the entire disclosure of which is incorporated by reference herein. This Application also claims priority of Italian Patent Application Serial No. MI2003A000820, filed April 18, 2003, the entire disclosure of which is incorporated by reference herein.--

AMENDMENTS TO THE CLAIMS

1. (Original) Rosiglitazone maleate crystalline form I having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.570	11.6687	2.4
8.580	10.2972	5.2
9.355	9.4458	8.1
14.005	6.3183	6.4
15.125	5.8529	41.4
16.005	5.5330	100.0
17.160	5.1631	10.0
18.625	4.7601	31.0
20.240	4.3838	6.8
21.000	4.2268	13.9
21.990	4.0387	32.9
22.785	3.8996	12.1
23.585	3.7691	30.0
25.055	3.5512	60.4
26.480	3.3632	18.0
28.425	3.1374	11.9
28.905	3.0863	8.6
30.430	2.9351	8.1
31.395	2.8470	6.7
32.145	2.7823	8.9
33.990	2.6353	9.3

2. (Original) Rosiglitazone maleate crystalline form having a powder diffraction spectrum to X-rays as shown in Figure 4.

3. (Original) Rosiglitazone maleate crystalline form I having a DSC graph as shown in Figure 1.

4. (Original) Rosiglitazone maleate crystalline form I having an IR spectrum as shown in Figure 7.

5. (Original) Rosiglitazone maleate crystalline form II having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.615	11.5998	7.4
8.985	9.8340	4.8
9.740	9.0733	9.3
13.635	6.4889	11.6
14.015	6.3138	7.1
15.320	5.7788	100.0
17.105	5.1796	43.8
17.910	4.9485	21.8
19.255	4.6058	16.7
20.330	4.3646	27.8
20.765	4.2741	21.7
22.285	3.9859	37.8
23.730	3.7464	14.1
24.610	3.6144	37.7
25.485	3.4922	27.0
27.030	3.2960	24.4
27.440	3.2477	17.0
28.135	3.1690	8.7
29.225	3.0533	12.7
29.905	2.9854	24.1
31.645	2.8251	11.5

6. (Original) Rosiglitazone maleate crystalline form II having a powder diffraction spectrum to X-rays as shown in Figure 5.

7. (Original) Rosiglitazone maleate crystalline form II having a DSC graph as shown in Figure 2.

8. (Original) Rosiglitazone maleate crystalline form II having an IR spectrum as shown in Figure 8.

9. (Original) Rosiglitazone maleate crystalline form III having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.555	11.6918	6.2
8.895	9.9333	9.0
9.670	9.1388	12.1
13.050	6.7785	5.7
15.030	5.8896	55.2
15.345	5.7694	100.0
16.970	5.2205	40.3
17.300	5.1216	30.3
17.810	4.9761	34.7
19.105	4.6416	16.9
20.060	4.4227	33.0
20.745	4.2782	27.4
22.190	4.0028	51.0
24.400	3.6450	52.1
25.205	3.5304	36.7
25.830	3.4464	13.4
26.675	3.3391	46.0
27.360	3.2570	26.3
27.985	3.1857	13.2
29.795	2.9961	35.5
30.685	2.9112	11.4

10. (Original) Rosiglitazone maleate crystalline form III having a powder diffraction spectrum to X-rays as shown in Figure 6.

11. (Original) Rosiglitazone maleate crystalline form III having a DSC graph as shown in Figure 3.

12. (Original) Rosiglitazone maleate crystalline form III having an IR spectrum as shown in Figure 9.

13. (Original) Pharmaceutical compositions containing rosiglitazone maleate crystalline form I according to claim 1 together with pharmaceutically acceptable excipients and/or adjuvants.

14. (Original) Pharmaceutical compositions comprising rosiglitazone maleate crystalline form II according co claim 5 together with pharmaceutically acceptable excipients and/or adjuvants.

15. (Original) Pharmaceutical compositions containing rosiglitazone maleate crystalline form III according to claim 9 together with pharmaceutically acceptable excipients and/or adjuvants.

16. (Currently Amended) A process for the crystallization of rosiglitazone maleate form I characterized in that it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in a solvent selected from alcohols, esters and/or ethers;

b. cooling said mixture to ambient temperature;

c. filtration and washing of the product;

d. desiccation.

17. (Original) A process according to claim 16, characterized in that said alcohols and/or esters are selected from isopropanol, ethyl acetate, isopropyl acetate and/or THF.

18. (Original) A process for the crystallization of rosiglitazone maleate form II, characterized in that it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in waver;

b. cooling said mixture to ambient temperature;

c. filtration and washing of the product;

d. desiccation.

19. (Original) A process for the crystallization of rosiglitazone maleate form II, characterized in that it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in a water:ethanol mixture from 1.5 : 1 to 2.5 : 1 by volume;

b. cooling said mixture to ambient temperature;

c. filtration and washing of the product;

d. desiccation.

20. (Original) A process for the crystallization of rosiglitazcne maleate form III characterized in that it comprises the following steps:

a. heating to reflux a mixture approximately containing rosiglitazone base and a double molar quantity of maleic acid in absolute ethanol and/or denatured ethanol;

b. cooling said mixture to ambient temperature;

c. filtration and washing of the product;

d. desiccation.

21. (Currently Amended) A process according to claims 16 [to 20], characterized in that said mixture is maintained
under reflux for a time ranging between about 20 and 40 minutes.

22. (New) A process according to claim 17, characterized in that said mixture is maintained under reflux for a time ranging between about 20 and 40 minutes.

23. (New) A process according to claim 18, characterized in that said mixture is maintained under reflux for a time ranging between about 20 and 40 minutes.

24. (New) A process according to claim 19, characterized in that said mixture is maintained under reflux for a time ranging between about 20 and 40 minutes.

25. (New) A process according to claim 20, characterized in that said mixture is maintained under reflux for a time ranging between about 20 and 40 minutes.

REMARKS

The specification was amended to include reference to priority applications.

Amendments to the claims were made in order to correct multiple dependencies and a typographical error in claim 16. No new matter has been added.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Dated: April 16, 2004

Respectfully submitted,

By MARIE GILFILLAN 44085
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Attorneys/Agents For Applicant

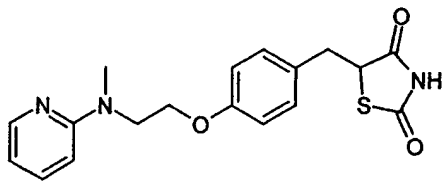
Polymorphous forms of rosiglitazone maleate

FIELD OF THE INVENTION

The present invention relates to the synthesis and characterization of three polymorphous forms of rosiglitazone maleate.

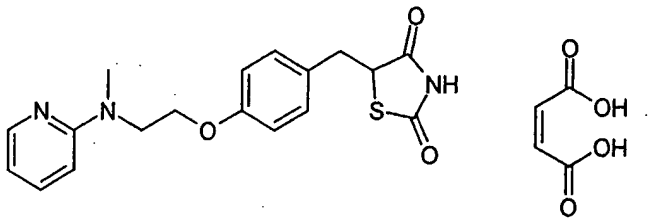
STATE OF THE ART

Rosiglitazone is a molecule of thiazolidinedione structure which forms part of the class of antidiabetics. Its structure formula is given below.



US 5,002,953 describes for the first time the compound and its use as an antihyperglycaemic. In that patent all its pharmaceutically acceptable salts are also claimed.

US 5,741,803 instead specifically describes the maleate of rosiglitazone, shown below, stating that among the possible salts, the maleate exhibits particularly favourable characteristics of stability and solubility in water.



In that patent, two examples of the preparation of the salt in question are given. In the first example the compound is prepared by hot dissolution of the rosiglitazone base mixed with maleic acid, and slow

precipitation of the salt derived therefrom. After treatment of the suspension at 0-5°C for several hours, a product is isolated which, when dried under vacuum at 50°C provides a product having a melting point (m.p.) of 120-121°C. The ^{1}H-NMR of the product is provided in which a wide band between 2 and 5 ppm is found which the applicant attributes to the residual water contained in the solvent (not otherwise specified). In the second example the maleate of rosiglitazone is treated, in ethanol, with an equivalent of maleic acid, while hot, until dissolution of the solid is obtained, the mixture is decoloured with carbon and the product is precipitated by cooling to 0-5°C, then the product is filtered and desiccated, having at the end of the treatments a m.p. of 119-119.5°C.

US 6,515,132 relates to a method for the synthesis of rosiglitazone maleate, in which the step of formation of the maleate of rosiglitazone is carried out in acetone.

Polymorphic forms of rosiglitazone maleate are disclosed in WO0064892, WO0064893, WO0064896 and WO0226737 whereas WO9931093, WO9931094 and WO9931095 describe the preparation of hydrates of rosiglitazone maleate.

DESCRIPTION OF THE INVENTION

It is known in fact that many organic compounds and their salts may exist in the form of a plurality of different crystalline structures, which exhibit different physical properties and may exhibit differences also from the biological point of view.

In the course of experiments on crystallization of the maleate of rosiglitazone it was surprisingly found that this salt, under specific conditions, crystallizes in

three different polymorphic crystalline pure forms, that have not been described before.

Obtaining pure crystalline forms is extremely useful, both because through these a precise characterization of the chemical-physical properties is possible, and because these characteristics may prove more favourable from a pharmacological point of view.

The subject of the present patent application are therefore three new polymorphous forms of rosiglitazone maleate, and also the methods necessary for the crystallization of these polymorphic forms.

DETAILED DESCRIPTION OF THE INVENTION

Tests on the synthesis of rosiglitazone maleate carried out starting from equimolar amounts of rosiglitazone base and maleic acid surprisingly led to the identification and characterization of two polymorphous crystalline forms of the aforesaid salt. Moreover by crystallizing mixtures of rosiglitazone base and double equimolar quantities of maleic acid a third polymorph of rosiglitazone maleate is obtained.

In particular, it was found that the maleate of rosiglitazone exists in three polymorphous crystalline modifications, which may be easily distinguished both by means of DSC, and IR, and also X-ray diffraction.

Rosiglitazone maleate exists in a polymorphous form I, which with the DSC exhibits an endothermic peak with maximum at 119°C (Figure 1), in a polymorphous form II, which with the DSC exhibits an endothermic peak with maximum at 121°C (Figure 2), and in a polymorphous form III which with the DSC exhibits an endothermic peak at 124°C (Figure 3) The DSCs were carried out with a Perkin Elmer DSC7 Differential Scanning Calorimeter.

The three forms have a powder diffraction spectrum to X-rays characterized by the principal absorptions

reported in Tables 1, 2 and 3 corresponding to Figures 4, 5 and 6, respectively (Radiation Cu Kα, Generator voltage 40 kV, Divergence Slit 1°, Receiving slit 0.2 mm, scan mode step start angle 5,000, End angle 35,000, time per step 2,000 sec):

FORM I (Table 1)

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.570	11.6687	2.4
8.580	10.2972	5.2
9.355	9.4458	8.1
14.005	6.3183	6.4
15.125	5.8529	41.4
16.005	5.5330	100.0
17.160	5.1631	10.0
18.625	4.7601	31.0
20.240	4.3838	6.8
21.000	4.2268	13.9
21.990	4.0387	32.9
22.785	3.8996	12.1
23.585	3.7691	30.0
25.055	3.5512	60.4
26.480	3.3632	18.0
28.425	3.1374	11.9
28.905	3.0863	8.6
30.430	2.9351	8.1
31.395	2.8470	6.7
32.145	2.7823	8.9
33.990	2.6353	9.3

FORM II (Table 2)

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.615	11.5998	7.4
8.985	9.8340	4.8
9.740	9.0733	9.3
13.635	6.4889	11.6
14.015	6.3138	7.1
15.320	5.7788	100.0
17.105	5.1796	43.8
17.910	4.9485	21.8
19.255	4.6058	16.7
20.330	4.3646	27.8
20.765	4.2741	21.7
22.285	3.9859	37.8
23.730	3.7464	14.1
24.610	3.6144	37.7
25.485	3.4922	27.0
27.030	3.2960	24.4
27.440	3.2477	17.0
28.135	3.1690	8.7
29.225	3.0533	12.7
29.905	2.9854	24.1
31.645	2.8251	11.5

FORM III (Table 3)

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.555	11.6918	6.2
8.895	9.9333	9.0
9.670	9.1388	12.1
13.050	6.7785	5.7
15.030	5.8896	55.2
15.345	5.7694	100.0
16.970	5.2205	40.3
17.300	5.1216	30.3
17.810	4.9761	34.7
19.105	4.6416	16.9
20.060	4.4227	33.0
20.745	4.2782	27.4
22.190	4.0028	51.0
24.400	3.6450	52.1
25.205	3.5304	36.7
25.830	3.4464	13.4
26.675	3.3391	46.0
27.360	3.2570	26.3
27.985	3.1857	13.2
29.795	2.9961	35.5
30.685	2.9112	11.4

The X-ray diffractions were carried out with a Philips PW3710 X-ray Diffractometer.

Form I exhibits with IR characteristic absorptions at the following wavelengths (Figure 7): 1744; 1618; 1262; 1178; 1083; 1070; 997, 823; 778 cm^{-1}.

Form II exhibits with IR the following characteristic absorptions (Figure 8): 1757; 1610; 1162; 1062; 1030; 926; 835; 767 cm^{-1}.

Form III, on the other hand, exhibits with IR the following characteristic absorptions (Figure 9): 1756; 1585; 1010; 921cm^{-1}.

The IR spectra were carried out with a Perkin Elmer 16 PC FT-IR spectrometer.

The solid-state ^{13}C-NMR spectra of Forms I, II and III, obtained with a Varian 400 Unity Inova, are reported in figures 10, 11, 12 and in the following tables 4, 5 and 6, respectively:

Chemical shifts (ppm):

FORM I (Table 4)

178.5	168.1	145.4	133.0	51.5
173.9	158.9	139.1	130.7	41.1
172.5	157.6	137.1	64.5	37.2
169.7	151.3	135.1	57.6	

FORM II (Table 5)

177.3	166.6	151.2	133.4	114.5	63.6	51.2
175.7	158.3	147.1	131.0	113.3	57.2	42.0
172.8	157.7	138.0	117.9	109.6	55.3	40.2
169.4	153.2	136.7	115.6	66.7	52.8	37.1

FORM III (Table 6)

177.4	166.4	151.2	130.9	113.3	63.6	51.1
175.8	158.4	146.9	117.9	112.0	57.4	42.0
172.9	157.6	138.0	115.7	109.6	55.2	40.2
169.5	153.3	136.6	114.5	66.3	52.8	36.9

Rosiglitazone maleate may be obtained in the form of the single polymorph I by blending an approximately equimolar mixture of rosiglitazone base and maleic acid in a series of solvents and mixtures thereof, which comprises isopropanol, acetone, ethyl acetate, isopropyl acetate, THF, by heating the suspension to reflux temperature of the solvent, followed by cooling of the mixture to ambient temperature. In this way a crystalline suspension of the product is obtained which, when filtered, washed and desiccated under vacuum for 12 hours at 45-50°C provides rosiglitazone maleate form I as the single crystalline form, as confirmed by IR, XRD and DSC analyses.

Form II of rosiglitazone maleate, however, may be obtained in a pure form by treatment of the approximately equimolar mixture of rosiglitazone base and maleic acid in water under reflux, followed by cooling of the mixture to ambient temperature. The solid suspended in the mixture may be filtered, washed and desiccated under vacuum for about 10 to 14 hours, preferably 12 hours, at 45-50°C and consists exclusively of crystals of Form II of rosiglitazone maleate.

Alternatively Form II of rosiglitazone maleate may be prepared by mixing approximately equimolar quantities of rosiglitazone base and maleic acid in a water:ethanol mixture from 1.5 : 1 to 2.5 : 1 by volume, preferably 2 : 1, under reflux, followed by cooling of the mixture to ambient temperature. The solid suspended in the mixture may be filtered, washed and desiccated under vacuum for about 10 to 14 hours.

Form III of rosiglitazone maleate on the other hand may be obtained in a pure form by crystallization of rosiglitazone base and a double molar quantity of

maleic acid in absolute ethanol or denatured ethanol. The mixture of the starting materials is brought to reflux, where a solution is obtained and it is then slowly cooled to room temperature; the crystalline solid thus formed is filtered, washed and dried and consists exclusively of crystals of Form III of rosiglitazone maleate.

The following experimental examples provide further clarification of the invention itself and in no way constitute any limitation thereof.

EXAMPLE 1

Synthesis of Rosiglitazone maleate Form I.

A 250 ml balloon flask equipped with mechanical stirring, coolant and thermometer, is charged with 10 g (28.0 mmoles) of rosiglitazone base, 3.25 g (28.0 mmoles) of maleic acid and 75 ml of isopropanol. The mixture is brought to reflux and maintained for 30' under such conditions. The mixture is then slowly cooled to ambient temperature and the product is filtered on a Buchner filter, washing twice with 10 ml of isopropanol. The filtered product is then desiccated for 12 hours at 45-50°C. 9.7 g of rosiglitazone maleate Form I (yield 73%) are obtained. The content of residual isopropanol in the product is 0.16% by weight.

EXAMPLE 2

Synthesis of Rosiglitazone maleate Form II.

A 500 ml balloon flask is charged with 20 g (56.0 mmoles) of rosiglitazone base and 6.50 g (56.0 mmoles) of maleic acid. To these solids are added 350 ml of water, and the mixture obtained is brought to reflux for 30'. The mixture is then slowly cooled to ambient temperature and the resultant solid is filtered on a Buchner filter, washing twice with 20 ml of water each

time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 19.9 g (yield 75%) and consists of rosiglitazone maleate Form II. The water content of the desiccated product is 0.3%.

EXAMPLE 3

Synthesis of rosiglitazone Form I.

Example 1 is repeated, using isopropyl acetate as solvent in place of the isopropanol. After desiccation, 9.5 g of rosiglitazone maleate Form I (yield 72%) are obtained.

EXAMPLE 4

Synthesis of Rosiglitazone maleate Form III.

A 500 ml balloon flask is charged with 15 g (42.0 mmoles) of rosiglitazone base and 9.70 g (84.0 mmoles) of maleic acid. To these solids are added 150 ml of ethanol, and the mixture obtained is brought to reflux for 30'. The mixture is then slowly cooled to ambient temperature and the resultant solid is filtered on a Buchner filter, washing twice with 20 ml of ethanol each time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 14.9 g (yield 75%) and consists of rosiglitazone maleate Form III.

EXAMPLE 5

Synthesis of Rosiglitazone maleate Form II.

A 500 ml balloon flask equipped with reflux condenser and dropping funnel is charged with 20 g (56.0 mmoles) of rosiglitazone base and 330 ml of deionised water. In a becker are charged 6.50 g (56.0 mmoles) of maleic acid and 23 ml of deionised water, whereby a solution is formed. The solution obtained is then charged in the dropping funnel. The suspension of rosiglitazone base in water is heated to reflux and from the dropping

funnel the solution of maleic acid is added in approximately 5'. The mixture is then slowly cooled to ambient temperature and the resultant solid is filtered on a Buchner filter, washing twice with 20 ml of water each time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 20.5 g (yield 77%) and consists of rosiglitazone maleate Form II. The water content of the desiccated product is 0.4%.

EXAMPLE 6

Synthesis of Rosiglitazone maleate Form II.

A 500 ml balloon flask is charged with 20 g (56.0 mmoles) of rosiglitazone base and 6.50 g (56.0 mmoles) of maleic acid. To these solids are added 160 ml of water and 80 ml of absolute ethanol. The mixture obtained is brought to reflux for 30' to obtain a clear solution. The solution is filtered on a panel of celite and allowed to cool to ambient temperature. The resultant solid is filtered on a Buchner filter, washed twice with 20 ml of water each time. A product is discharged which when desiccated under vacuum at 45-50°C for 12 hours weighs 21.0 g (yield 79%) and consists of rosiglitazone maleate Form II. The water content of the desiccated product is 0.3%.

C L A I M S

1. Rosiglitazone maleate crystalline form I having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.570	11.6687	2.4
8.580	10.2972	5.2
9.355	9.4458	8.1
14.005	6.3183	6.4
15.125	5.8529	41.4
16.005	5.5330	100.0
17.160	5.1631	10.0
18.625	4.7601	31.0
20.240	4.3838	6.8
21.000	4.2268	13.9
21.990	4.0387	32.9
22.785	3.8996	12.1
23.585	3.7691	30.0
25.055	3.5512	60.4
26.480	3.3632	18.0
28.425	3.1374	11.9
28.905	3.0863	8.6
30.430	2.9351	8.1
31.395	2.8470	6.7
32.145	2.7823	8.9
33.990	2.6353	9.3

2. Rosiglitazone maleate crystalline form I having a powder diffraction spectrum to X-rays as shown in Figure 4.

3. Rosiglitazone maleate crystalline form I having a DSC graph as shown in Figure 1.

4. Rosiglitazone maleate crystalline form I having an IR spectrum as shown in Figure 7.

5. Rosiglitazone maleate crystalline form II having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.615	11.5998	7.4
8.985	9.8340	4.8
9.740	9.0733	9.3
13.635	6.4889	11.6
14.015	6.3138	7.1
15.320	5.7788	100.0
17.105	5.1796	43.8
17.910	4.9485	21.8
19.255	4.6058	16.7
20.330	4.3646	27.8
20.765	4.2741	21.7
22.285	3.9859	37.8
23.730	3.7464	14.1
24.610	3.6144	37.7
25.485	3.4922	27.0
27.030	3.2960	24.4
27.440	3.2477	17.0
28.135	3.1690	8.7
29.225	3.0533	12.7
29.905	2.9854	24.1
31.645	2.8251	11.5

6. Rosiglitazone maleate crystalline form II having a powder diffraction spectrum to X-rays as shown in Figure 5.

7. Rosiglitazone maleate crystalline form II having a DSC graph as shown in Figure 2.

8. Rosiglitazone maleate crystalline form II having an IR spectrum as shown in Figure 8.

9. Rosiglitazone maleate crystalline form III having a powder diffraction spectrum to X-rays with the following principal absorptions:

Angle (2θ)	d (Å)	Rel. Intens. (I/I_0)
7.555	11.6918	6.2
8.895	9.9333	9.0
9.670	9.1388	12.1
13.050	6.7785	5.7
15.030	5.8896	55.2
15.345	5.7694	100.0
16.970	5.2205	40.3
17.300	5.1216	30.3
17.810	4.9761	34.7
19.105	4.6416	16.9
20.060	4.4227	33.0
20.745	4.2782	27.4
22.190	4.0028	51.0
24.400	3.6450	52.1
25.205	3.5304	36.7
25.830	3.4464	13.4
26.675	3.3391	46.0
27.360	3.2570	26.3
27.985	3.1857	13.2
29.795	2.9961	35.5
30.685	2.9112	11.4

10. Rosiglitazone maleate crystalline form III having a powder diffraction spectrum to X-rays as shown in Figure 6.

11. Rosiglitazone maleate crystalline form III having a DSC graph as shown in Figure 3.

12. Rosiglitazone maleate crystalline form III having an IR spectrum as shown in Figure 9.

13. Pharmaceutical compositions containing rosiglitazone maleate crystalline form I according to claim 1 together with pharmaceutically acceptable excipients and/or adjuvants.

14. Pharmaceutical compositions containing rosiglitazone maleate crystalline form II according to claim 5 together with pharmaceutically acceptable excipients and/or adjuvants.

15. Pharmaceutical compositions containing rosiglitazone maleate crystalline form III according to claim 9 together with pharmaceutically acceptable excipients and/or adjuvants.

16. A process for the crystallization of rosiglitazone maleate form I characterized in that it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in a solvent selected from alcohols, esters and/or ethers;

b. cooling said mixture to ambient temperature;

c. filtration and washing of the product;

d. desiccation.

17. A process according to claim 16, characterized in that said alcohols and/or esters are selected from isopropanol, ethyl acetate, isopropyl acetate and/or THF.

18. A process for the crystallization of rosiglitazone maleate form II, characterized in that it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in water;

b. cooling said mixture to ambient temperature;

c. filtration and washing of the product;

d. desiccation.

19. A process for the crystallization of rosiglitazone maleate form II, characterized in that it comprises the following steps:

a. heating to reflux an approximately equimolar mixture of rosiglitazone base and maleic acid in a water:ethanol mixture from 1.5 : 1 to 2.5 : 1 by volume;

b. cooling said mixture to ambient temperature;

c. filtration and washing of the product;

d. desiccation.

20. A process for the crystallization of rosiglitazone maleate form III characterized in that it comprises the following steps:

a. heating to reflux a mixture approximately containing rosiglitazone base and a double molar quantity of maleic acid in absolute ethanol and/or denatured ethanol;

b. cooling said mixture to ambient temperature;

c. filtration and washing of the product;

d. desiccation.

21. A process according to claims 16 to 20, characterized in that said mixture is maintained

under reflux for a time ranging between about 20 and 40 minutes.

Polymorphous forms of rosiglitazone maleate

Abstract

Three new polymorphous crystalline forms of rosiglitazone maleate, termed respectively form I, II and III and the methods for selectively obtaining each form are described and characterized. Rosiglitazone maleate may be obtained in the form of the single polymorph I by blending an approximately equimolar mixture of rosiglitazone base and maleic acid in a series of solvents and mixtures thereof which comprises isopropanol, acetone, ethyl acetate, isopropyl acetate, THF, followed by cooling of the mixture to ambient temperature; the form II may on the other hand be obtained by means of treatment of the approximately equimolar mixture of rosiglitazone base and maleic acid in water under reflux, followed by cooling of the mixture to ambient temperature; the polymorph III may be obtained by treating a mixture of rosiglitazone base with a double molar quantity of maleic acid in ethanolic solvents.

Application Data Sheet

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